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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,072	04/03/2007	Siegfried Ansorge	PMP-0003	6887

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EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
12/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,072	ANSORGE ET AL.	
	Examiner	Art Unit	
	CHRIS E. SIMMONS	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8 and 10-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8 and 10-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 09/24/2008, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Objections

Claim 7 is objected to because of the following informalities: "is" should be changed to "are". Appropriate correction is required.

Duplicate Claims

Applicant is advised that should claims 7 or 8 be found allowable, claims 10 or 11, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112 - New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-8, 10-11 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 recites the limitation "a combination consisting of (a) silibinin or a salt thereof, (b) alpha-lipoic acid or a salt thereof, and *a pharmaceutical carrier for each (a) and (b).* The limitation, "a pharmaceutical carrier for each (a) and (b)", is considered to introduce new matter because there is not adequate support for this limitation insofar as the broad claim of "a pharmaceutical carrier". It is suggested that "a pharmaceutical carrier" be replaced by "an additive which is an aqueous solvent, a stabilizer, a suspending agent, a dispersing agent or a wetting agent".

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession

of the claimed invention. Claim 5 recites the limitation "...wherein (a), (b), **and (c)** are administered to said subject by inhalation in a simultaneous, **separate**, or timed manner". This newly added limitation is considered to introduce new matter because there is no adequate support for the claimed method where (c), i.e., an additive, is administered separate from (a) and (b).

Claim Rejections - 35 USC § 103

Claims 1-3, 5-8 and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biewenga et al. (Arch. Biochem. Biophys. (1994);312(1):114-20) in view of Mira et al. (Biochem. Pharmacol. (1994);48(4):753-9), the combination further taken in view of US 2004/0167153 .

The primary reference discloses that hypochlorous acid (HOCL) is an oxidant that has a prominent effect in inactivation or alpha-1-anti-proteinase. Due to this inactivation, the ability of the anti-proteinase to inhibit elastase is lost. The resulting higher activity of elastase is held responsible for tissue damage in lung emphysema. It further discloses that lipoic acid possesses HOCL-scavenging activity. *See abstract.* The reference does not expressly teach silibinin or inhalation.

The secondary reference discloses that silibinin dihemisuccinate (SDH) is also an HOCL scavenger. It additionally discloses that a compound that is a good HOCL scavenger of HOCL will protect alpha-1-anti-proteinase against inactivation by HOCL over the concentration range present *in vivo.* The reference further discloses that even

micromolar concentrations of SDH in buffer solution were able to protect alpha-1-anti-proteinase from HOCL. It is known that when SDH is administered in a dose of 5 mg/kg, a concentration of 50 micrograms/mL (68.8 micromolars) is reached at the end of a 2-hr infusion. Thus, SDH may scavenge HOCL at a rate fast enough to protect important targets *in vivo*, such as alpha-1-anti-proteinase. *See pg, 758, 1st full para.* The results presented in the reference, when combined with the knowledge that silibinin has low toxicity, support a potential role for silibinin as an antioxidant drug. *See page 758, last full sentence in 1st column.* The reference does not expressly teach lipoic acid or inhalation.

The tertiary reference discloses combination therapy using aerosol or dry powder formulations [0110] for simultaneous, sequential or separate administration by the inhaled route in the treatment of obstructive airways or other inflammatory disease, such as asthma or emphysema [0065] (abstract). The reference does not expressly teach alpha-lipoic acid or silibinin.

It would have been obvious at the time of the invention to one of ordinary skill in the art to protect damage to lung cells of chronically obstructed lungs, such as emphysemic lungs, by administering a composition through inhalation, wherein the composition consists of silibinin, alpha-lipoic acid and a pharmaceutically acceptable carrier. The skilled artisan would have been motivated to combine silibinin with alpha-lipoic acid by the desire to use the HOCL scavenging qualities of both compounds to prevent HOCL from ultimately increasing the tissue damaging properties of elastase since this elastase activity is considered responsible for lung damage in emphysema.

The artisan would also have a reasonable expectation to, at least, render an additive scavenger effect against HOCL by using these compounds together in combinatory therapy. Generally, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose; the idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980): In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960). Conversely, there is no evidence in the record establishing the Applicant's combination of agents is any more effective or in any way different than any single member of that combination. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964). In this case, both alpha-lipoic acid and silibinin are known as effective HOCL scavengers that would protect anti-1-proteinase from inactivation.

As for the claimed dosages, it is known in the art of pharmaceutical therapy that drug dosages can be calculated and adjusted depending on many different factors, such as, inter alia, weight, sex, age, frequency of administration, the form of the medication and channel of administration[1]. Generally, it is not patentable to optimize the concentration of ingredients in a composition through routine experimentation. Differences in concentration from what is disclosed in the reference, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. It is not inventive to discover the optimum or

[1] Walter Arthur Bastedo - "Factors Which Modify the Dose", pp.48-52. (Materia Medica: Pharmacology, Therapeutics and Prescription Writing for Students and Practitioners; W. B. Saunders company (1918)) - discloses some of the many factors that would affect dosage amounts in the pharmaceutical treatment of

workable ranges by routine experimentation. *See MPEP 2144.05 [R-5] II A.* Accordingly, varying dosage amounts is an obvious step in the treatment of subjects who vary in weight or age, for example.

Conclusion

No claims are allowed.

Pertinent art not relied upon for the current Office Action:

- Tarjan et al. (Eur. J. Repir. Dis. (1983);64(6):442-8) - discloses prevention of elastase-induced emphysema by aerosol administration of an elastase inhibitor (title).
- Seeto et al. (Aust. Fam. Physician (2001);30(6):557-61) - discloses that inhalation therapy is the most effective drug administration route for the treatment of asthma and COPD. A metered-dose inhaler is an acceptable alternative to nebulizers in most cases. The reference does not expressly teach silibinin or lipoic acid.

Conclusion

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a subject. Factors include: age, sex, weight, time of administration, frequency of administration, form of

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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remedy, and channel of administration (pp. 48-52).

/C. E. S./
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612